REMARKS

Upon entry of the present Amendment, Claims 1-6, 13-16 and 49-51 are pending and under consideration. A clean copy of the claims as currently pending is attached hereto as Appendix A.

I. THE AMENDMENT TO THE SPECIFICATION

The specification has been amended to clarify that risk for coronary artery disease is suggested by previous or current vascular surgery or the presence of at least two cardiac risk factors. Support for the amendment to the specification can be found, for instance, in Mangano *et al.*, JAMA 268:233-239 (incorporated by reference in the specification as originally filed at page 12, line 11, and at page 19, lines 17-18). Since the amendment to the specification is fully supported by the specification as originally filed, entry thereof is respectfully requested.

II. THE AMENDMENTS TO THE CLAIMS

Claims 1 and 49 have been amended to recite a method wherein a cardiovascular agent is administered to a patient in the period starting immediately after surgery and ending when symptoms of cardiovascular stress are reduced. Support for the amendments to Claims 1 and 49 can be found in the specification at, for example, page 12, lines 9-10, and at, for example, page 12, lines 18 to 20. Claim 49 has additionally been amended to correct a minor error in claim language. The amendments to Claims 1 and 49 do not constitute new matter. Entry of the amendments is therefore respectfully requested.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-6, 13-16 and 49-52 stand rejected under 35 U.S.C. § 112, as allegedly being indefinite. The Examiner contends that upper limits should be recited in the recitations of heart rate and blood pressure in Claims 1 and 49. Applicant respectfully traverses the rejection. .

Determining whether a claim is definite requires an analysis of whether one of skill in the art would understand the bounds of the claim when read in light of the specification. *Personalized Media Communicatoins LLC v. ITC*, 48 USPQ2d 1880, 1888

(Fed. Cir. 1998). If the claims read in light of the specification reasonably apprise those of skill in the art of the scope of the invention, § 112 demands no more. *Id.*

Claims 1 and 49 recite methods of administering a pharmacologic cardiovascular agent to a patient while the patient's heart rate is greater than or equal to 65 bpm and the patient's systolic blood pressure is greater than or equal to 100 mm Hg. One of skill in the art would readily recognize that each patient has a maximum heart rate and that the methods of Claims 1 and 49 are naturally bounded by the upper limit of the patient's maximum heart rate. Furthermore, one of skill in the art would readily recognize that the pharmacologic cardiovascular agents used in the claimed methods reduce heart rate. Thus, no heart rate is too high for administration. As such, one of skill in the art would understand that the bounds of the claims include administration of the agent when the patient's heart rate is greater than or equal to 65 bpm and less or equal to the patient's maximum heart rate.

Similarly, the methods of Claims 1 and 49 are naturally bounded by the upper limit of the patient's maximum blood pressure. In addition, since the pharmacologic cardiovascular agents used in the claimed methods reduce blood pressure, no blood pressure is too high for administration. Thus, one of skill in the art would also understand that the bounds of the claims include administration of the agent when the patient's blood pressure is greater than or equal to 100 mm Hg and less than or equal to the patient's maximum blood pressure.

Since one of skill in the art would understand the bounds of Claims 1 and 49, Applicant submits that the claims are definite. Applicant respectfully requests that the rejection of Claims 1-6, 13-16 and 49-52 under 35 U.S.C. § 112, second paragraph, be withdrawn.

IV. REJECTION UNDER 35 U.S.C. §103(a)

Claims 1-6, 13-16, and 49-52 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Goldstein *et al.*, 1993, *J. Cardiovasc. Pharmacol.* 22(2):253-8 ("Goldstein"). The rejection is respectfully traversed on the ground that Goldstein is not sufficient to establish a *prima facie* case of obviousness against the claims.

A. The Legal Standard

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d. 1443, 1444 (Fed. Cir. 1992). In order to establish *prima facie* obviousness, three basic criteria must be met.

First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the Examiner. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Alternatively, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. *See id.* The mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Examiner would succeed. *In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Royka*, 180 USPQ 580 (CCPA 1974). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

If any one of these criteria are not met, *prima facie* obviousness is not established, and Applicants are not required to show new or unanticipated results or objective indicia of nonobviousness. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

B. Goldstein Fails to Teach or Suggest Each and Every Element of Claims 1-6, 13-16, and 49-52

Each and every element of Claims 1-6, 13-16, and 49-52 are not taught or suggested by Goldstein. Amended Claim 1, and Claims 2-6, 13-16, and 50-52 which depend therefrom, recite methods for reducing cardiovascular disease complications in a patient following surgery comprising the step of administering to the patient a pharmacologic cardiovascular agent after surgery near the maximum effective dose of the agent while certain conditions are met. The agent is administered daily in the period after surgery while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm. Independent Claim 49 recites a similar method. Goldstein does not teach or suggest each and every element of Claims 1-6, 13-16, and 49-52.

First, Goldstein does not teach or suggest the administration of an agent near its maximum effective dose. The methods of Claims 1-6, 13-16, and 49-52 recite an aggressive dose of a pharmacologic cardiovascular agent near its maximum effective dose. The maximum effective oral dose of atenolol is about 100 mg/day or more depending upon the patient (*see* specification at page 13, line 15; *see also* Physician's Desk Reference and Goodman and Gilman's, The Pharmacological Basis of Therapeutics, both incorporated by reference in the specification at page 19, lines 17-18). In contrast, Goldstein teaches a single, conservative dose of 50 mg atenolol. The conservative 50 mg dose of atenolol in Goldstein does not teach or suggest the aggressive therapy of the methods of Claims 1-6, 13-16, and 49-52.

Second, according to the claimed methods, the agent is administered daily to provide continuous coverage in the full period beginning immediately after surgery. Significantly, the agent is administered even during the period when a patient is not able to take oral medication. Coverage of this period is important because one-half or more of the most severe cardiovascular stress occurs immediately following surgery. According to the methods of Claims 1-6, 13-16 and 49-51, the agent can be administered intravenously, for

example, during this period. In contrast, Goldstein teaches a method of administering a dose of 50 mg of atenolol, an amount that can only be administered orally because the maximum intravenous dose of atenolol is about 10 mg/day (*see* specification at, for example, page 9, lines 25-26; *see also* Physician's Desk Reference and Goodman and Gilman's, The Pharmacological Basis of Therapeutics, both incorporated by reference in the specification at page 19, lines 17-18). However, in the period following surgery, especially following coronary artery bypass surgery as taught by Goldstein, oral absorption of an agent is poor. As a result, Goldstein does not teach administration of an agent in the period immediately following surgery. The method taught by Goldstein thus does not teach or suggest administration of an agent during the full period following surgery and especially during the critical period immediately following surgery.

Finally, the Examiner concedes that Goldstein's fails to disclose the absence of congestive heart failure, third degree heart block or bronchospasm, and specific heart rate and blood pressure reading at the time of dosing, as recited in Claims 1-6, 13-16 and 49-52. Nevertheless, the Examiner contends that these conditions would have been obvious because patients not meeting these criteria are routinely excluded as candidates for atenolol therapy. Applicant submits that these conditions are not obvious end points for therapy. For instance, the administration of agents such as atenolol is not contraindicated for all patients that evidence symptoms of congestive heart failure and bronchospasm. In fact, atenolol has been used for treatment of patients with heart failure and for patients with a history of bronchospasm. The Examiner also contends that a heart rate at or slightly above 65 bpm and a systolic blood pressure slightly over 100 mm Hg is within the "normal range" for administration. Applicant submits that safe and effective heart rate and blood pressure ranges for administration of a pharmacologic cardiovascular agent to patients *in the period following surgery* were not known prior to the present invention. The Examiner has provided no evidence that teaches or suggests administration of a pharmacologic cardiovascular agent in the period following surgery when the patient's heart rate is greater than or equal to 65 bpm and when the patient's systolic blood pressure is greater than or equal to 100 mmHg.

Since the Examiner has not pointed out any teaching or suggestion of the administration of an aggressive dose of a pharmacologic agent, any teaching or suggestion of administration in the full period following surgery, any teaching or suggestion of continuous

administration, or any teaching or suggestion of the recited conditions of administration, the Examiner has failed to make out a *prima facie* case of obviousness.

C. The Field of Management of Perioperative Risk of Coronary Artery Disease Long Felt a Need for Guidelines for Perioperative Assessment and Management of Risk from Coronary Artery Disease

Even assuming, *arguendo*, that the Examiner has made out a *prima facie* case of obviousness, objective evidence of nonobviousness thoroughly rebuts the Examiner's *prima facie* case of obviousness.

Even if *prima facie* obviousness is established, an applicant can rebut the *prima facie* showing of obviousness with arguments and/or evidence demonstrating the nonobviousness of the claimed invention. *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Rebuttal evidence may include objective evidence of nonobviousness such as commercial success, long felt but unsolved needs or failure of others. *Graham v. John Deere Co.*, 383 US 1, 17, 148 USPQ 459, 467 (1966).

Applicant submits that an addendum to the Clinical Guideline of the American College of Physicians, attached as Exhibit 1, provides clear evidence that the field of perioperative assessment and management of risk from coronary artery disease long felt a need for the development of guidelines for treatment that has been filled by the present invention. Palda *et al.*, 1997, *Ann. Intern. Med.* 127:313-328 ("Palda"). At page 313, Palda states that clinicians frequently need to evaluate the perioperative risk status of their patients and that members of the American College of Physicians rated perioperative assessment as one of ten topics most in need of guideline development. According to Palda, the field perioperative assessment of risk of coronary artery disease was filled with confusion. Palda's extensive search of the literature revealed few management strategies other than coronary revascularization. Palda at 322-3.

note Exhibit 42 - not state of the art at time of the invention

However, after reviewing the contemporary recommendations for assessment and management of perioperative risk from coronary artery disease, Palda, in an addendum at page 323, hails Mangano *et al.*, 1996, N. Engl. J. Med. 335:1713-20, ("Mangano *et al.*", attached as Exhibit 2), as "an important publication" that "should alter current practice." Mangano *et al.* describes aspects of the claimed methods. The methods of Mangano *et al.*, according to Palda, can substantially reduce mortality rates and rates of nonfatal cardiac events. Palda, in these Clinical Guidelines of the American College of Physicians, concludes

that the results provided in Mangano *et al.* are sufficiently convincing to give atenolol to noncardiac surgery patients at risk for coronary artery disease according to the methods of Mangano *et al.* Thus, according to the objective evidence of Palda, the field of management of perioperative risk of coronary artery disease long felt a need for effective methods of assessment and management, a need that was unsolved prior to the present invention. Therefore, even assuming *arguendo* that the Examiner has established a *prima facie* case of obviousness, the objective evidence of Palda demonstrates the nonobviousness of the invention.

Applicant therefore respectfully requests that the rejection of Claims 1-6, 13-16, and 49-52 under 35 U.S.C. § 103(a) be withdrawn.

V. CONCLUSION

Applicant submits that Claims 1-6, 13-16, and 49-52 meet all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-6, 13-16, and 49-52 to issuance is therefore kindly solicited.

Applicant estimates that no fee in addition to the fee for the extension of time is due with this response. However, the Commissioner is authorized to charge any underpayment or credit any overpayment to the deposit account No. 16-1150 for any matter in connection with this response which may be required.

Respectfully submitted,

650-493 4935 (Palo Alto)

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Rahul Pathak (Reg. No.)

For: Samuel B. Abrams (Reg. No. 30,605)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Appendix A
Claims After Entry of Amendment

1. A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: administering to the patient a pharmacologic cardiovascular agent after surgery near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm wherein the pharmacologic agent is administered daily in the period from immediately after surgery until symptoms of cardiovascular stress are reduced.

2. The method of Claim 1 in which the agent is administered daily in the period after surgery until hospital discharge.

3. The method of Claim 2 in which the agent is administered daily in the period after surgery for at least three days.

4. The method of Claim 2 in which the agent is administered daily in the period after surgery for up to seven days.

5. The method of Claim 1 in which the agent is a β_1-adrenergic selective blocking agent.

6. The method of Claim 5 in which the agent is atenolol.

7. The method of Claim 1 in which the agent is an α-2 agonist.

8. The method of Claim 1 in which the agent is a nitrate.

9. The method of Claim 1 in which the agent is a calcium channel blocker.

10. The method of Claim 1 in which the agent is an ACE inhibitor.

11. The method of Claim 1 in which the agent is a platelet inhibitor.

12. The method of Claim 1 in which the agent is a thrombosis inhibitor.

13. The method of Claim 1 in which the surgery is cardiac-related surgery.

14. The method of Claim 1 in which the surgery is non-cardiac-related surgery.

15. The method of Claim 1 in which the patient suffers from coronary artery disease.

16. The method of Claim 1 wherein the patient is at risk for coronary artery disease.

49. (Amended) A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: continuously administering to the patient a pharmacologic cardiovascular agent after surgery wherein the agent is

a) continuously administered in the period from immediately after surgery until symptoms of

cardiovascular stress are reduced near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm; or

b) continuously administered in the period from immediately after surgery until symptoms of cardiovascular stress are reduced at about one half of the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 55 bpm, but less than 65 bpm, while the patient's systolic blood pressure is greater than 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.

50. The method of Claim 1 in which the patient has had previous vascular surgery, or is undergoing current vascular surgery, or has at least two of the following cardiac risk factors: older than 65 years, hypertensive, current smoker, serum cholesterol level of at least 6.2 mmol/L, or diabetes mellitus.

51. The method of Claim 1 in which the agent is atenolol and the maximum effective dose is about 100 mg/day orally or about 10 mg BID intravenously.